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Childhood acute lymphoblastic leukemia: Immunophenotypic profile and aberrant expression of CD13, CD33, CD117, CD11b, CD16, and CD64

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Abstract:

BACKGROUND: Childhood acute lymphoblastic leukemia (ALL) is the most prevalent malignant disease (25%–30%) and the most common type of leukemia (75%–80%) among children. It is not a single disease with significant phenotypic and genotypic variability that has diagnostic and prognostic implications. This study aims to provide the immunophenotypic profile of childhood ALL in Iraqi patients and to explore the frequency of aberrant myeloid antigen expression and their association with hematological parameters.

PATIENTS, MATERIALS AND METHODS: The records of 67 pediatric patients diagnosed as ALL were reviewed for their flow cytometric immunophenotyping results at presentation.

RESULTS: B-ALL constituted 76.1% of the cases and 23.9% were T-ALL. There was a highly significant statistical relation between higher age interval and T-ALL phenotypes (P = 0.001). Higher hemoglobin (Hb) level and white blood cell count were significantly related with T-ALL subtype (P = 0.039 and < 0.001, respectively). CD34, HLA-DR, CD10, and CD79a were significantly correlated with B-ALL compared to T-ALL (P = 0.007, <0.001, <0.001, and <0.001, respectively). With no significant differences, aberrant myeloid antigen expression was found in 51% of B-ALL and in 25% of T-ALL cases; however, CD34 expression was substantially related with aberrant myeloid antigen expression (P = 0.001).

CONCLUSION: Aberrant myeloid antigens were expressed in 44.9% of ALL patients with insignificant differences between B- and T-ALL phenotypes. CD34 was significantly associated with B-lineage ALL and with aberrant myeloid antigen expression. T-ALL children are older and have significantly higher Hb concentration and white blood cell count. No correlation was found between aberrant myeloid expression and hematological parameters in B-ALL.

Keywords:
Acute lymphoblastic leukemia, immunophenotyping, aberrant expression

Introduction

Acute lymphoblastic leukemia (ALL) is a malignant disorder that originates in a single B- or T-lymphocyte progenitor. Proliferation and accumulation of clonal blast cells in the marrow result in suppression of hematopoiesis and, thereafter, anemia, thrombocytopenia, and neutropenia. The disease is most common in children but can be seen in individuals of any age.[1] In the early classification schemes, French–American–British (FAB) classification was based mainly on cytomorphology supplemented by immunohistochemistry.[2] The World Health Organization classification emphasizes the use of immunophenotyping for accurate categorization of ALL cases. FAB classification has no prognostic or therapeutic implications.[3] Leukemic

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cells from patients with ALL express a variety of differentiation antigens that are also found on normal lymphocyte precursors at discrete stages of maturation.[4] Most leukocyte antigens lack lineage specificity; hence, a panel of antibodies is needed to establish the diagnosis and to distinguish among the different immunologic subclasses of leukemic cells. Flow cytometric immunophenotyping of childhood ALL plays an important role not only in the diagnosis and classification of B- and T-cell lineages but also in predicting the outcome.[2] Immunophenotyping by means of multichannel flow cytometry has become the standard procedure for ALL diagnosis and subclassification, and was also developed as a useful tool for the detection and monitoring of minimal residual disease. This study aims to provide the immunophenotypic profile of childhood ALL in Iraqi patients and to explore the frequency of aberrant myeloid antigen expression and their association with hemoglobin (Hb) level, and white blood cell (WBC) and platelet counts.

Patients, Materials, and Methods

A retrospective descriptive study included 67 pediatric newly diagnosed ALL patients aged ≤16 years who were admitted to Children Welfare Teaching Hospital, Medical City, in Baghdad. The diagnosis was based on morphology, cytochemistry, and flow cytometric immunophenotyping done on peripheral blood and/or bone marrow aspirate samples. Panels of fluorochrome-conjugated monoclonal antibodies (BD Biosciences kits) were used. Data acquisition and sample analysis were performed on BD FACS-Canto™ II (6-color, Becton Dickinson Company, USA), using BD FACS-Canto Diva, after calibration with the BD CaliBRITE™ beads.

The panels were as follows:

- Pan-leukocyte marker CD45
- Primary panel included immature markers (CD34, TdT, HLA-DR, and CD38) and lineage markers to allow the classification of most cases into the broad categories of myeloid (MPO+), B-cell (CD19+), or T-cell (cCD3 + and CD7+)[5]
- Secondary panel of antibodies is necessary to define the blast differentiation and maturation stage as follows: [5]
  - For B-ALL: CD79a, CD20, CD10, and SmIg
  - For T-ALL: CD1a, CD2, sCD3, CD4, CD5, CD8, and CD56
  - For myeloid cells: CD13, CD33, CD117, CD16, and CD11b
  - For monocytic cells: CD14 and CD64.

The blast gating strategy included using dot plots of CD45 expression (forward scatter) versus intracellular complexity (side scatter). A total of 10,000 events were acquired in the target gate.[3] Antigen expression was considered to be positive when the percentage of positive blast cells is ≥20%, except for MPO, CD3, CD79a, and TdT, which are considered positive at the 10% level of expression.[6]

ALL cases were classified immunologically according to Vora A[1] with minor modifications as follows:

Bases of ALL immunological classification used in this study

ALL subtype	CD marker expression
• B-cells lineage:	CD19+
• Pro-B:	CD10–, TdT+
• Early pre-B and Pre-B:	CD10+
• Mature B cell (Burkitt):	SmIg+, TdT–
T-cell lineage:	cCD3+, CD7+
• Early (ETP):	CD1a–, sCD3–
• Mid (Cortical):	CD1a+
• Late (Mature):	sCD3+, CD1a–

TdT= Terminal deoxynucleotidyl transferase, SmIg= Surface membrane immunoglobulin, ETP= Early T-cell precursor.

The study was approved by the Scientific Council of Pathology in the Iraqi Board for Medical Specializations and was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Data analysis was undertaken using Statistical Package for Social Sciences version 20, Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. Categorical data were presented in the form of frequencies and percentages. Pearson's Chi-square and Fisher exact tests were used to evaluate nominal variable frequency difference between groups. The level of <0.05 was considered significant for the interpretation of *P* values.

Results

The mean age of ALL patients ± standard deviation was 6.8 ± 4.7 years with a median of 5 years. The majority of ALL patients, 48/67 (71.6%), were aged <10 years; 42/51 (82.4%) of B-ALL, and 6/16 (37.5%) of T-ALL. There was a highly significant statistical relation between higher age and T-ALL phenotypes (P = 0.001). Hb level and WBC count were higher in T-ALL, showing statistically significant differences with P values of 0.039 and <0.001, respectively [Table 1]. The overall male-to-female ratio was

Table 1: Hematological parameters in 67 B- and T-acute lymphoblastic leukemia patients

Hematological parameters	Levels	Phenotype		Total, *n* (%)	*P**
		B-ALL, *n* (%)	T-ALL, *n* (%)		
Hb (g/dL)	<7	14 (27.5)	2 (12.5)	16 (23.9)	0.039
	7-11	28 (54.9)	8 (50.0)	36 (53.7)	
	>11	9 (17.6)	6 (37.5)	15 (22.4)	
WBC (×109/L)	<50	43 (84.3)	3 (18.8)	46 (68.7)	<0.001
	≥50	8 (15.7)	13 (81.2)	21 (31.3)	
Platelet (×109/L)	<100	41 (80.4)	14 (87.5)	55 (82.1)	0.409
	≥100	10 (19.6)	2 (12.5)	12 (17.9)	
Total		51 (100)	16 (100)	67 (100)	

*Chi-square test (Fisher's exact test). Hb=Hemoglobin, WBC=White blood cell, ALL=Acute lymphoblastic leukemia

Table 2: The expression frequency of various CD markers in 67 patients of acute lymphoblastic leukemia

CD markers	Positive markers			*P**
	In B-ALL (*n*=51), *n* (%)	In T-ALL (*n*=16), *n* (%)	Total (*n*=67), *n* (%)	
CD34	42 (82.4)	7 (43.8)	49 (73.1)	0.007
HLA-DR	51 (100)	1 (6.3)	52 (77.6)	<0.001
TdT	42 (82.4)	10 (62.5)	52 (77.6)	0.096
CD38	41 (80.4)	13 (81.3)	54 (80.6)	0.940
cCD3	0	16 (100)	16 (23.9)	<0.001
sCD3	0	7 (43.8)	7 (10.5)	<0.001
CD1a	1 (2)	7 (43.8)	8 (11.9)	<0.001
CD2	2 (3.9)	12 (75)	14 (20.9)	<0.001
CD4	1 (2)	8 (50)	9 (13.4)	<0.001
CD5	1 (2)	14 (87.5)	15 (22.4)	<0.001
CD7	0	16 (100)	16 (23.9)	<0.001
CD8	0	13 (81.3)	13 (19.4)	<0.001
CD56	2 (3.9)	0	2 (3)	0.421
CD19	51 (100)	0	51 (76.1)	<0.001
CD10	44 (86.3)	3 (18.8)	47 (70.1)	<0.001
CD20	18 (35.3)	0	18 (26.9)	0.005
CD79a	43 (84.3)	1 (6.3)	44 (65.7)	<0.001
SmIg	0	0	0	-
Aberrant myeloid antigen expression (A patient may express more than one aberrant antigen)				
CD13	16 (31.4)	2 (12.5)	18 (26.9)	0.137
CD33	11 (21.6)	1 (6.3)	12 (17.9)	0.163
CD16	10 (19.6)	1 (6.3)	11 (16.4)	0.208
CD11b	3 (5.9)	0 (0)	3 (4.5)	0.321
CD117	1 (2)	1 (6.3)	2 (3)	0.379
CD15	0	0	0	-
MPO	0	0	0	-
CD14	0	0	0	-
CD64	0	0	0	-
CD13 + 33	4 (7.8)	1 (6.3)	5 (7.5)	-
CD11b + 16	1 (2)	0	1 (1.5)	-
CD33 + 16	1 (2)	0	1 (1.5)	-
CD13 + 16	1 (2)	0	1 (1.5)	-
CD13 + 11b + 16	1 (2)	0	1 (1.5)	-
CD13 + 33 + 117	1 (2)	0	1 (1.5)	-
CD13 + 33 + 16	2 (3.9)	0	2 (3)	-

*Pearson Chi-square (Asymptotic significance two-sided), **The percentages are calculated out of each category. ALL=Acute lymphoblastic leukemia, HLA-DR=Human leukocyte antigen-DR isotype, TdT=Terminal deoxynucleotidyl transferase, SmIg=Surface membrane immunoglobulin, MPO=Myeloperoxidase

1.9:1 (in B-ALL, 1.5:1; in T-ALL, 4.3:1). In 67 ALL patients, 51 (76.1%) were B-ALL and 16 (23.9%) were T-ALL.

CD34, HLA-DR, CD10, and CD79a were significantly correlated with B-ALL compared to T-ALL with *P* values of 0.007, <0.001, <0.001, and <0.001, respectively [Table 2]. HLA-DR expression was seen in all B-lineage cases, while only one case of T-lineage ALL was positive for this marker. TdT was more expressed in B-ALL patients than T-ALL but with insignificant difference ($P = 0.096$). Furthermore, CD38 also showed an almost equal percentage of expression in both phenotypes with insignificant differences.

Seven cases of B-ALL showed aberrant expression of T-lineage markers: CD2 (2), CD56 (2), CD1a (1), CD4 (1), and CD5 (1). In T-ALL, three cases expressed CD10 and one case showed expression of CD79a marker.

Aberrant myeloid marker expression (CD13, CD33, CD16, CD11b, and CD117 in descending manner) was seen in 44.8% of the total ALL cases with no statistically significant differences between the two phenotypes. Aberrant myeloid antigen expression was positive in 26/51 cases (51%) of B-ALL, the most common was CD13 (31.4%) followed by CD33 (21.6%), CD16 (19.6%), CD11b (5.9%), and CD117 (2%). Co-expression of markers was seen in 11 cases; four of them expressed two markers (CD13 and CD33) and only one case for each of the following two markers: CD11b and CD16, CD33 and CD16, and CD13 and CD16, while co-expression of three markers (CD13, CD33, and CD16), (CD13, CD33, and CD117), and (CD13, CD11b, and CD16) was seen in two, one, and one case, respectively. In T-ALL, the aberrant myeloid antigen expression was positive in 4/16 cases (25%), one of them showed co-expression of CD13 and CD33.

Aberrant myeloid antigen expression was significantly associated with CD34 expression ($P = 0.001$), whereas no significant associations were found with TdT and HLA-DR [Table 3].

Comparison of various cutoff levels of hematological parameters in B-ALL cases between the presence and absence of aberrant myeloid antigen expression showed insignificant differences in the frequencies [Table 4].

Among the B-ALL subtypes, the CD10-positive group was the most frequently encountered in 86.3% (44/51) of cases. Unfortunately, due to the unavailability of cytoplasmic immunoglobulin (cIg), the distinction between early pre-B-ALL and pre-B-ALL subtypes was not feasible. Pro-B subtype was present in 7 cases (13.7%), and depending on blast cell morphology and absence of SmIg, no mature B-ALL cases were observed in this study [Table 5].

Table 3: The relations between nonlineage specific markers and aberrant myeloid antigen expression in 67 acute lymphoblastic leukemia patients

CD marker	Aberrant myeloid antigens		*P**
	Positive (*n*=30), *n* (%)	Negative (*n*=37), *n* (%)	
CD34	28 (93.3)	21 (56.8)	0.001
TdT	25 (83.3)	27 (73.0)	0.385
HLA-DR	26 (86.7)	26 (70.3)	0.145

*Chi-square test (Fisher's exact test). TdT= Terminal deoxynucleotidyl transferase, HLA-DR= Human leukocyte antigen-DR isotype

Table 4: The frequencies of 51 B-acute lymphoblastic leukemia cases with and without aberrant myeloid markers in different hematological parameters

Hematological parameters	Levels	B-ALL with aberrant myeloid antigens expression		Total, *n* (%)	*P**
		n=26 positive, *n* (%)	*n*=25 negative, *n* (%)		
Hb (g/dL)	<7	7 (26.9)	7 (28.0)	14 (27.5)	0.889
	7-11	15 (57.7)	13 (52.0)	28 (54.9)	
	>11	4 (15.4)	5 (20.0)	9 (17.6)	
WBC (×109/L)	<50	20 (76.9)	23 (92.0)	43 (84.3)	0.139
	≥50	6 (23.1)	2 (8.0)	8 (15.7)	
Platelets (×109/L)	<100	21 (80.8)	20 (80.0)	41 (80.4)	0.945
	≥100	5 (19.2)	5 (20.0)	10 (19.6)	
Total		26 (100)	25 (100)	51 (100)	

*Pearson Chi-square (Asymptotic significance two-sided), *P* value is significant if <0.05. Hb=Hemoglobin, WBC=White blood cell, ALL=Acute lymphoblastic leukemia

Table 5: The frequencies of immunophenotypic subtype in 67 acute lymphoblastic leukemia cases with and without aberrant myeloid markers

ALL subtypes	Total, *n* (%)	Aberrant myeloid antigens expression (*n*=30)	
		Positive	Negative
B-lineage	51	26	25
Pro-B	7 (13.7)	3	4
Early pre-B	44 (86.3)	23	21
Pre-B			
Mature B-cell (Burkitt)	0		
T-lineage	16	4	12
Early	6 (37.5)	3	3
Mid (cortical)	7 (43.75)	1	6
Late (mature)	3 (18.75)	0	3

In T-ALL subtypes, cortical T-ALL was the most frequent and presented in 43.75% (7/16) of cases followed by early T-ALL (37.5%), then mature ALL (18.75%).

Aberrant myeloid antigen expression was not observed in mature T-ALL and no mature B-ALL was recorded.

Discussion

The relation between T-ALL and higher age group was comparable with other studies;[7,8] however it is quite different from others.[9-11] Those results revealed that the majority of B-ALLs were detected within favorable age group, although the three cases <1-year-old (unfavorable age group) were of B-ALL phenotype (2 males and 1 female, all were negative for aberrant myeloid markers), whereas many of T-ALLs were detected within unfavorable age group.

WBC count of 50 × 10^9/L is generally used as an operational cutoff point between better and poorer prognoses.[12] The results of WBCs count in B-and T-ALL subtypes at initial diagnosis were similar to those obtained from Bachir *et al*.[9] and Pui *et al*.[13] studies, while they were not in line with Supriyadi *et al*.[11] This result clarifies that majority of B-ALLs patients had WBCs counts ranging within favorable limits (<50 × 10^9/L), whereas majority of T-ALLs patients had WBCs counts within the unfavorable limits (≥50 × 10^9/L). Highly significant correlation between WBC count and phenotypes was seen. These results confirm the close association between T-cell phenotype with older age, male gender, and higher leukocyte count.[1]

In the study population, the prevalence of B-ALL was three times greater than T-ALL, this finding is quite comparable to other studies, as reported by Noronha *et al*.[14] in Brazil, Supriyadi *et al*.[15] in Indonesia, Bachir *et al*.[9] in Morocco, Kamal *et al*.[16] in Jordan, and Hunger and Mullighan[17] in which the prevalence of T-ALL was forming 27.1%, 23%, 21.2%, 20.7%, and 15%, respectively. CD10 and CD34 expressions were both significantly higher in B-ALL cases than in T-ALL, and many studies have issued the influence of its expression or its co-expression with CD34 over treatment outcome and overall survival.[18] In assigning B-lineage to T-lineage cells, CD79a and CD10 should not be considered since both can also be expressed by T lymphoblasts.[19]

Aberrant myeloid antigen expression in ALL subtypes can be detected in as many as half of the cases. However, this expression has no prognostic implications but can be used to distinguish leukemic cells from normal progenitor cells, thereby enabling the detection of minimal residual leukemia.[20] The frequency of aberrant myeloid expression in ALL identified in this study was similar to the Lopes *et al*.[7] study in Brazilian patients (49.2%), and 52.4% by Bachir *et al*.[9] and 53.2% by Tanyeli *et al*.[21] Other studies done by Kavianpour *et al*.[22] and Silva *et al*.,[23] showed a frequency of approximately (31%). Lower frequencies were identified by Shahni *et al*. (22%),[24] Gupta *et al*. (23%),[25] and Supriyadi *et al*. (25%),[11] while the highest frequency (88.5%) was reported by Seegmiller *et al*.[26] One potential reason for this variation is differences in the binding characteristics of different monoclonal antibody clones, different thresholds for

antigen positivity, and different flow cytometry methods, instruments, and reagents may also play a role.[26]

The frequency of myeloid co-expression was higher in B-ALL cases than in T-ALL cases, this result is comparable to Bachir *et al*.[9] and Noronha *et al*.;[14] however, they are higher than that shown by Cuéllar-Mendoza *et al*.[20] The differences observed are probably due to the criteria used to define a "percent positive" cell and the number of antigens tested.

A significant association was demonstrated between co-expression of CD34 and aberrant myeloid antigen, this is comparable with what had been shown by Sharma *et al*.[27] The value of this association needs to be further investigated, as CD34 expression has been linked with prognosis in many studies.[28] Immunophenotyping may be related to particular cytogenetic patterns, but this needs larger studies to confirm.[29]

There is higher WBC and lower platelet counts in myeloid positive B-ALL cases, these findings are in agreement with results of other studies.[7,15] Despite these variations, there was no statistically significant difference observed between the conventional and aberrant myeloid expression cases in regard to leukocyte count, Hb concentration and platelet count. The discrepancies between studies may be related to the use of different treatment protocols.[30] The association between hematological prognostic factors and aberrant phenotypes in ALL in children remains controversial.[31]

Conclusion

CD13, CD33, CD117, CD11b, and CD16 are aberrantly expressed, in descending manner, in 44.9% of ALL patients, but did not show significant differences between B- and T-ALL phenotypes. However, aberrant myeloid antigen expression was significantly associated with CD34 expression. Children with T-ALL phenotypes are associated with higher age group, Hb level, and WBC count. No correlation was found between aberrant myeloid expression and hematological parameters in B-ALL.

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Conflicts of interest
There are no conflicts of interest.

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